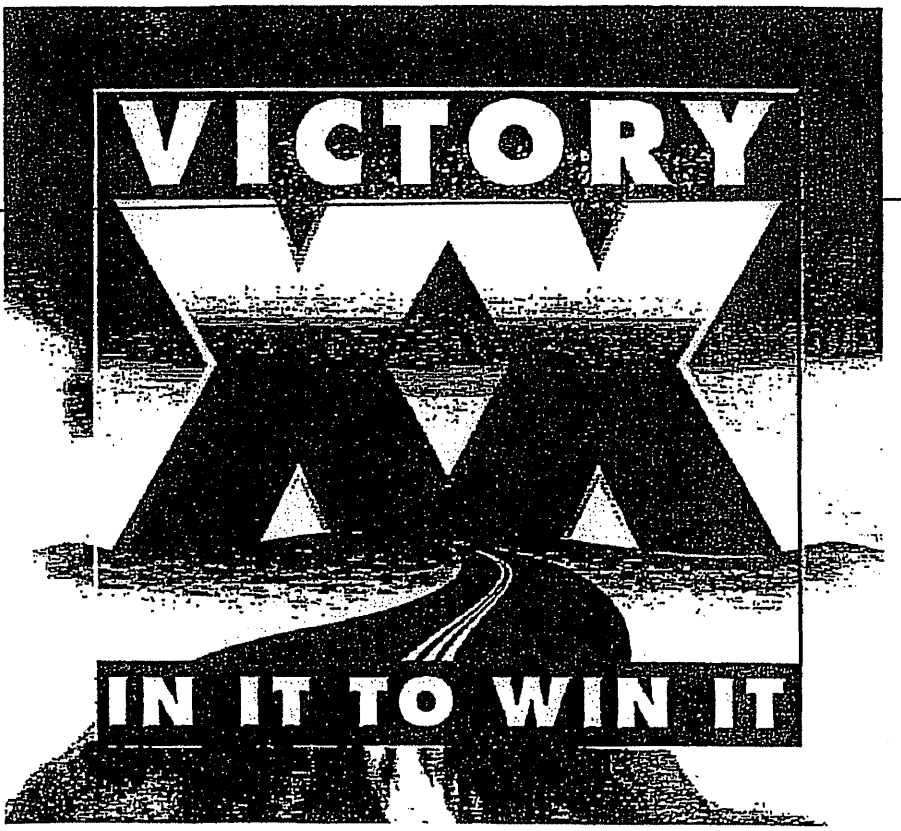
OBSTACLE RESPONSE GUIDE VIOXX®



INFLAMMATORY MANAGEMENT BULLETIN: OBSTACLE RESPONSE GUIDE

TO:
Field Sales Team for VIOXX®

PURPOSE:
To provide you with the initial Obstacle Response Guide. Over time we will be providing you updates and modifications to this resource.

CONTENT:
You are all aware of the process identified for resolving obstacles:

- Pause
- Clarify the Question
- Verify your Understanding of the Issue
- Resolve & Return to the Core Messages

Let's take just a moment to focus on the clarification of the issue. As we launch VIOXX®, we have entered into a very competitive marketplace. Our competition has been aggressively "pre-positioning" our product. This is likely to generate obstacles or issues that need to be resolved before some customers are comfortable prescribing the product for appropriate patients. It will be critical that we clarify the issue prior to attempting to resolve. Many times, the customer may be vague in their statement, such as "I understand VIOXX® has some safety concerns at higher doses." Statements like this could apply to three different issues, methotrexate, warfarin or edema. Unless you clarify, you might respond regarding edema when the physicians concern was warfarin. This approach would actually result in you creating an additional obstacle for yourself.

Some customers may be hesitant to state their true concerns and will use obstacles as a "smokescreen". They hope to distract or redirect you in an attempt to end a product discussion. Again, clarification will be critical. One honest obstacle effectively handled is a tremendous opportunity. Obstacles should be viewed as selling opportunities. Essentially the customer is saying, "I would prescribe if only I knew....." and when you resolve this question, you have earned the right to ask for appropriate patients.

A few final quotes regarding obstacles and the obstacle handling step in selling:

"Obstacles are those frightful things you see when you take your eyes off your goals" – *Unknown*

"The difference between the right words and the almost right words, is the difference between a lightening bolt and a lightening bug." – *Mark Twain*

"Wise people take the complicated and make it simple and understandable." – *Einstein*

"No problem can stand the assault of sustained thinking." – *Voltaire*

"Chance favors the prepared mind." – *Louis Pasteur*

Remember the final step in effective obstacle resolution is to return to the core selling messages of the product. As you review this Obstacle Response Guide, take time to practice both resolving the issue, transition back to your messages and closing the call.

ACTION REQUIRED:
We will be counting on you for two important steps in this process:

1. Identify the issues you are encountering on territory that require a response
2. Effectively implement the responses to resolve the concerns expressed by your customers.

Good Luck and GOOD SELLING!

Obstacles / Responses

1. "There is no difference between VIOXX® and Celebrex. Why should I use VIOXX®?"

Clarify: Doctor, while they both work by inhibiting COX-2, I would like to point out some key clinical areas of distinction that may be important to you and your patients.

INDICATIONS

Once daily VIOXX® is indicated for the relief of the signs and symptoms of OA, management of acute pain in adults and treatment of primary dysmenorrhea, representing all of the indications that were submitted to the FDA for approval of VIOXX®.

Celecoxib is indicated for the signs and symptoms of OA and RA.

Reference:

A&A Training Program ⇒ Module 5 (NSAIDs)
VIOXX® PI ⇒ Indications and Usage (V22)
Celecoxib PI ⇒ Indications and Usage (C23)

CONTRAINDICATIONS

Both VIOXX® and celecoxib are contraindicated in patients who are allergic to them, aspirin or other NSAIDs. Once daily VIOXX® is not contraindicated in patients with sulfonamide allergies, commonly known as sulfa allergies.

In contrast, celecoxib is contraindicated in patients with allergic-type reactions to sulfonamides. This contraindication is unique to celecoxib, due to its molecular structure, and is **not a class effect**. Sulfonamide allergies are common drug allergies in the US population and allergic reactions can range from mild to more serious.

Once daily VIOXX® offers simplicity - simplified prescribing without having to worry about a sulfonamide allergy contraindication.

Reference:
VIOXX® PI ⇒ Contraindication (V23)
Celecoxib PI ⇒ Contraindication (C24)

DOSING
Doctor, VIOXX® offers dosing simplicity of once daily dosing for all indications – the relief of the signs and symptoms of OA, management of acute pain in adults, and the treatment of primary dysmenorrhea. With celecoxib, each time you see an OA patient you must decide whether to prescribe it once a day or twice a day. VIOXX® also offers the option to increase the dose to 25 mg once daily for OA patients who need additional relief. Celecoxib has one dose – 200 mg, and its label states that no additional efficacy is seen with 200 mg BID.

Reference:
~~VIOXX® PI ⇒ Dosage and Administration ⇒ Osteoarthritis (V65)~~ and Management of Acute Pain and Treatment of Primary Dysmenorrhea (V66)
Celecoxib PI ⇒ Dosage and Administration ⇒ Osteoarthritis (C54)

METABOLISM
Once daily VIOXX® is metabolized primarily through cytosolic enzymes in the liver. Unlike once daily VIOXX®, celecoxib is metabolized through the cytochrome P450 system.

(Remember to provide appropriate balancing information on use in hepatic insufficiency and hepatic effects.)

Reference:
VIOXX® PI ⇒ Clinical Pharmacology ⇒ Pharmacokinetics ⇒ Metabolism (V7)

COMPREHENSIVE CLINICAL STUDIES

Once daily VIOXX® has been comprehensively studied. In OA patients, once daily VIOXX® was compared to diclofenac in two 1-year studies. The endoscopy studies were six-month studies. We have data on serious upper GI events out to one year. This was the most comprehensive clinical program ever run by Merck. Let me share some of the data with you...

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Reference:
VIOXX® PI ⇒ Clinical Studies ⇒ OA (V16)

2. "I can't use VIOXX® with patients being treated with methotrexate."

Doctor, once daily VIOXX® is not contraindicated in patients receiving methotrexate. No dosage adjustments of once daily VIOXX® and no change in the standard monitoring for methotrexate are required for patients taking methotrexate with once daily VIOXX®.

If probed further:
Doctor, according to the product circular for once daily VIOXX®, at doses of 75 mg (which is 3 to 6 times the OA therapeutic dose), once daily VIOXX® increased plasma concentrations of methotrexate by 23%. At 24 hours post dose or at the trough period, a similar proportion of patients receiving VIOXX® or placebo had methotrexate plasma concentrations below the measurable limit. According to the methotrexate label, methotrexate-toxicity is believed to be more dependent on time of exposure rather than peak levels. Again doctor, no dosage adjustments of once daily VIOXX® and no change in the standard monitoring for methotrexate are required for patients taking methotrexate with once daily VIOXX®.

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Reference:
VIOXX® PI ⇒ Precautions ⇒ Drug Interactions ⇒ Methotrexate (V47)

3. "Is VIOXX® contraindicated in patients being treated with warfarin?"

No. Once daily VIOXX® is not contraindicated in patients taking warfarin and no change in standard monitoring is required. According to the package insert, when therapy with once daily VIOXX® is initiated or changed, patients should be monitored for INR* values. Doctor, the recommendation for once daily VIOXX® is the same recommendation for warfarin when any new therapy is initiated.

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If further probed, refer to the PI:
In a 21-day multiple-dose study in healthy individuals stabilized on warfarin (2 to 8.5 mg daily), administration of VIOXX® 25 mg QD was associated with mean increases in INR* of approximately 8% (range of INR on warfarin alone, 1.1 to 2.2; range of INR on warfarin plus VIOXX®, 1.2 to 2.4). Somewhat greater mean increases in INR of ~11% (range of maximum INR on warfarin alone, 1.5 to 2.7; range of maximum INR on warfarin plus VIOXX®, 1.6 to 4.4) were also seen in a single dose PK screening study using a 30-mg dose of warfarin and 50 mg of VIOXX®. Standard monitoring of INR values should be conducted when therapy with VIOXX® is initiated or changed, particularly in the first few days, in patients receiving warfarin or similar agents.

(Submit a PIR if appropriate.)

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Reference:
VIOXX® PI ⇒ Precautions ⇒ Drug Interactions ⇒ Warfarin (V51)

***INR** – International Normalized Ratios. This is a standardized way of measuring the degree of anti-coagulation produced by warfarin.

4. "I'm concerned about the potential edema that occurs with VIOXX®."

Clarify:
What are your specific concerns regarding edema?

If the physician's concern is the overall incidence of edema with once daily VIOXX®, then respond:
Doctor, edema is reported with all NSAIDs and is thought to result from cyclooxygenase inhibition in the kidney. Clinical trials with once daily VIOXX® 12.5 and 25 mg have shown renal effects such as edema similar to those observed with comparator NSAIDs. In these studies, the incidence rates for lower extremity edema were as follows: (In the AE table, point to row on edema under Body As A Whole)

VIOXX® 12.5 mg or 25 mg once daily - 3.7%
Ibuprofen 2400 mg – 3.8%
Diclofenac 150 mg –3.4%
Placebo – 1.1%

In clinical trials, the effects of edema were mild and there were no discontinuations due to edema.

If the physician's concern is the dose related increase of edema with once daily VIOXX® 50 mg, then respond:

Doctor, let me explain where the use of 50 mg is recommended. 50 mg is recommended for use in acute pain in adults. It has been studied for up to 5 days. In these studies, the renal effects of once daily VIOXX®– such as edema – were generally similar to comparator NSAIDs.

The 50 mg dose is not recommended for OA. However, in clinical trials with once daily VIOXX® 50 mg up to 6 months, there was a higher incidence of lower extremity edema.

Finally, let me point out that edema is reported with all NSAIDs and is thought to result from cyclooxygenase inhibition (COX-2) in the kidney.

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Reference:
VIOXX® PI ⇒ Adverse Reactions ⇒ OA ⇒ Table and second paragraph (V59)
VIOXX® PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)

5. "It is my understanding that VIOXX® was denied an indication for RA by the FDA."

Clarify: Doctor, what is your true concern?

If physician mentions denial of an RA indication, respond:
Doctor, Merck was not denied any indications. Once daily VIOXX® is indicated for relief of the signs and symptoms of OA, management of acute pain in adults, and for the treatment of primary dysmenorrhea. These represent all of the indications that Merck submitted to the FDA for the approval of once daily VIOXX®.

If appropriate, state: Last month when I was in, you stated that the majority of your arthritis patients suffer from OA. I would like for us to discuss how once daily VIOXX® could benefit these patients.

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(After close: If you need information on the use of VIOXX® in RA, I can submit a PIR.)

If the physician is concerned about the anti-inflammatory effect, see obstacle #6.

Reference:
VIOXX® PI ⇒ Indications and Usage (V22)
VIOXX® PI ⇒ Clinical Pharmacology ⇒ Mechanism of Action (V3)

6. "VIOXX® is not an anti-inflammatory drug."

Doctor, the Mechanism of Action section of the package insert for once daily VIOXX® clearly states: "VIOXX® is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and anti-pyretic activities in animal models." Once daily VIOXX® 12.5 and 25 mg reduced the signs and symptoms of OA as effectively as 2400 mg of ibuprofen. Also, once daily VIOXX® produced significant reductions in joint stiffness upon first awakening in the morning. Doctor, as you know, morning stiffness is one indicator of inflammation.

In addition, let me point out that in the label it also states "because of the anti-inflammatory effects of VIOXX®, the pharmacological activity of VIOXX® in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions."

Doctor, would you agree that once daily VIOXX® has anti-inflammatory effects?

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Reference:
VIOXX® PI ⇒ Clinical Pharmacology ⇒ Mechanism of Action (V3)
VIOXX® PI ⇒ Clinical Studies ⇒ OA (V16)
VIOXX® PI ⇒ Precautions ⇒ General (V31)

7. "Can VIOXX® be used in patients using low dose aspirin?"

Let me share with you the experience we have on the concomitant use of once daily VIOXX® and low-dose aspirin. At steady state, once daily VIOXX® 50 mg had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin.

I should also remind you that once daily VIOXX® is not a substitute for aspirin for cardiovascular prophylaxis and that concomitant administration of low-dose aspirin with once daily VIOXX® may result in an increased risk of GI ulceration or other complications compared with use of once daily VIOXX® alone.

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Reference:
VIOXX® PI ⇒ Precautions ⇒ Drug Interactions ⇒ Aspirin (V41)

8. "I understand that VIOXX® has sulfur as part of its chemical structure. Is it contraindicated for patients with "sulfa allergies?"

No. Doctor, let me show you the contraindications section of the label. Once daily VIOXX® is not contraindicated for patients with known sulfonamide allergies, commonly known as "sulfa allergies."

Unlike once daily VIOXX®, celecoxib is contraindicated in patients with sulfonamide allergies. Celecoxib contains a sulfonamide group ($S\text{-}NH_2$), which is associated with sulfa allergies. This contraindication is based on the specific chemical structure of celecoxib and is not a class effect. Sulfonamide allergies are common drug allergies in the US population and allergic reactions can range from mild to more serious.

Once daily VIOXX® offers simplicity, with no sulfonamide allergy contraindication.

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Reference:
VIOXX® PI ⇒ Contraindications (V23)

9. "Why wasn't VIOXX® 50 mg studied for longer than five days in acute pain?"

To obtain an indication for the management of acute pain in adults, all analgesic drugs are studied in short-term standard pain models as defined by the FDA. The maximum time for these studies for once daily VIOXX® was 5 days. However, let me point out that while it is not a recommended dose for OA, once daily VIOXX® 50 mg was studied out to 6 months. In these studies, the general safety profile of once daily VIOXX® 50 mg was similar to the recommended doses, except for a higher incidence of GI symptoms, lower extremity edema, and hypertension. Also, let me point out that once daily VIOXX® is indicated for the treatment of acute pain. The studies that support this acute pain indication lasted up to 5 days. But as I mentioned, while it is not a recommended OA dose, once daily VIOXX® 50 mg was studied for up to 6 months in OA patients – so the profile is well defined in the circular.

~~If further probed: "But, I'm worried about GI safety long-term."~~
Doctor, in two identical studies of OA patients receiving once daily VIOXX® 25 or 50 mg for up to 24 weeks, once daily VIOXX® demonstrated significantly fewer endoscopic ulcers than ibuprofen.

Once daily VIOXX® also has GI event data from clinical trials up to one year. Among 3,357 patients who were treated with once daily VIOXX® 12.5, 25, and 50 mg in controlled clinical trials of 6-weeks to 1 year, a total number of four patients experienced a serious upper GI event. Two patients experienced an upper GI bleed within 3 months (0.06%); one experienced an obstruction within 6 months; and one experienced an upper GI bleed within 12 months, for a total incidence of 0.12% over 1 year.

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Reference:
VIOXX® PI ⇒ Clinical Studies ⇒ Analgesic Studies (V17)
VIOXX® PI ⇒ Clinical Studies ⇒ OA (V16)

10. "Why didn't you compare VIOXX® to higher doses of ibuprofen or naproxen sodium for the management of pain?"

To obtain an indication for the management of acute pain in adults, a drug must be studied in standard pain models as defined by the FDA. As it states in the ibuprofen PI, in clinical studies using doses of ibuprofen greater than 400mg are no more effective than the 400mg dose in analgesia. Also, the maximum recommended dose of naproxen for analgesia is 550 mg.

In acute analgesic models of post-orthopedic surgical pain, post-operative dental pain and primary dysmenorrhea, once daily VIOXX® relieved pain that was rated by patients as moderate to severe. In post-surgical dental pain studies, the onset of action with a single 50mg dose of once daily VIOXX® occurred within 45 minutes.

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Reference:

VIOXX® PI ⇒ Clinical Studies ⇒ Analgesia (V17)

11. "When do I prescribe VIOXX® 12.5 mg, 25 mg, or 50 mg once daily?"

Whether you're treating OA or acute pain, once daily VIOXX® is always a simple once daily dose.

12.5 mg or 25 mg once daily for OA

Once daily VIOXX® 12.5mg is the starting dose for OA. If a patient requires greater pain relief, you have the flexibility to increase the dose to 25mg once daily at no additional cost to the patient.

50 mg once daily for Acute Pain and Primary Dysmenorrhea

In patients with moderate to severe acute pain, the dose is 50mg once daily. Once daily VIOXX® relieved moderate to severe pain following orthopedic surgery, dental surgery and primary dysmenorrhea.

In addition to the simplicity of once daily dosing, once daily VIOXX® also adds the flexibility of oral suspension for both strengths.

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Reference:
VIOXX® PI ⇒ Dosage and Administration (V65-V67)

12. "Can I use VIOXX® in patients with renal impairment?"

No dosage adjustment is recommended for patients with mild to moderate renal impairment. Use of once daily VIOXX® in patients with advanced renal disease is not recommended because no safety information is available regarding the use of once daily VIOXX® in these patients.

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Reference:
VIOXX® PI ⇒ Precautions ⇒ Renal Effects (V33)
VIOXX® PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)

13. "Why doesn't VIOXX® have a 50 mg tablet?"

Once daily VIOXX® is not offered in a single 50 mg tablet and a dosage of 50mg can be easily achieved by taking two 25 mg tablets.

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Reference:
VIOXX® PI ⇒ Dosage and Administration (V66)

14. "How does your price compare to Celebrex and other branded NSAIDs?"

Doctor, the catalog price for once daily VIOXX® is $2.02 for both 12.5 mg and 25 mg, offering your patients one of the best values available.

The catalog price for celecoxib is $2.38 for 100mg bid and $2.02 for 200 mg qd.

In addition, the catalog price for the oral suspension of once daily VIOXX® is competitive with other NSAIDs at $3.00.

This price comparison does not establish that products have comparable efficacy. These prices reflect direct cost and do not reflect actual costs paid by consumers.

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(For your reference, the average wholesale price (AWP) for once daily VIOXX® is $2.42 for both 12.5 mg and 25 mg. AWP for celecoxib is $2.86 for 100 mg BID and $2.42 for 200 mg qd. AWP for the oral suspension of once daily VIOXX® is competitive with other NSAIDs at $3.60.)

15. "Isn't a 17-hour half-life inconsistent with once daily dosing?"

The 17 hour half-life of once daily VIOXX® is entirely consistent with its once daily dosing. In all OA studies, lasting from 6 to 86 weeks with 3900 patients, once daily treatment with VIOXX® 12.5 and 25 mg in the morning was associated with a significant reduction in joint stiffness upon first awakening in the morning. At doses of 12.5 and 25 mg once daily, the effectiveness of once daily VIOXX® was shown to be comparable to ibuprofen 800mg TID and diclofenac 50 mg TID.

If probed further on half life:
Doctor, many drugs with half-lives shorter than 24 hour are effective when dosed once a day, for example Singulair, Prinivil, and Zocor.

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Reference:
VIOXX® PI ⇒ Clinical Pharmacology ⇒ Excretion (V8)
VIOXX® PI ⇒ Clinical Studies ⇒ OA (V16)
SINGULAIR® PI ⇒ Clinical Pharmacology ⇒ Excretion
PRINIVIL® PI ⇒ Clinical Pharmacology ⇒ Excretion
ZOCOR® PI ⇒ Clinical Pharmacology ⇒ Excretion